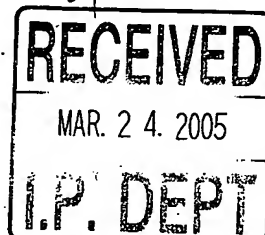


From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 72.2)

To:

KYOWA HAKKO KOGYO CO., LTD.
6-1, Ohtemachi 1-chome
Chiyoda-ku, Tokyo 100-8185
JAPON

Date of mailing (day/month/year) 17 March 2005 (17.03.2005)	
Applicant's or agent's file reference 1494	IMPORTANT NOTIFICATION
International application No. PCT/JP2003/008079	International filing date (day/month/year) 26 June 2003 (26.06.2003)
Applicant KYOWA HAKKO KOGYO CO., LTD. et al	

1. Transmittal of the translation to the applicant.

The International Bureau transmits herewith a copy of the English translation made by the International Bureau of the international preliminary examination report established by the International Preliminary Examining Authority.

2. Transmittal of the copy of the translation to the elected Offices.

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following elected Offices requiring such translation:

AZ, CA, CH, CN, CO, EP, GH, KG, KR, MK, MZ, RO, RU, TM

The following elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, BA, BB, BG, BR, BY, BZ, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, ES, FI, GB, GD, GE, GM, HR, HU, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. Reminder regarding translation into (one of) the official language(s) of the elected Office(s).

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report.

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Masashi Honda
Facsimile No.+41 22 740 14 35	Facsimile No.+41 22 338 70 10

Translation

PATENT COOPERATION TREATY

PCT/JP2003/008079



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1494	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP2003/008079	International filing date (day/month/year) 26 June 2003 (26.06.2003)	Priority date (day/month/year) 26 June 2002 (26.06.2002)
International Patent Classification (IPC) or national classification and IPC A61K 31/47, 31/496, 31/5377, 45/00, C07D 215/18, 215/42, 215/50, 215/52, A61P 1/00, 3/10, 9/00, 9/10, 9/12, 11/00, 13/12, 15/00, 19/10, 25/00, 25/04, 25/14, 25/16, 25/28, 29/00, 35/00, 37/02, 37/08, 43/00		
Applicant KYOWA HAKKO KOGYO CO., LTD.		

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>12</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of _____ sheets.</p>
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input checked="" type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input checked="" type="checkbox"/> Certain documents cited.</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>

Date of submission of the demand 25 December 2003 (25.12.2003)	Date of completion of this report 30 April 2004 (30.04.2004)
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/JP2003/008079

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 28-31, 33

because:

☒ the said international application, or the said claims Nos. 28-31, 33
relate to the following subject matter which does not require an international preliminary examination (*specify*):

SEE SUPPLEMENTAL SHEET

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 28-31, 33

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

The subject matter of claims 28 to 31 and 33 relates to methods for treatment of the human body by surgery or therapy. Thus, this International Preliminary Examining Authority is not required to carry out international preliminary examination on this subject matter.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

SEE SUPPLEMENTAL SHEET

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-27, 32

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/JP 03/08079

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

The chemical structure common among the compounds represented by the general formula (IA) described in claim 9 is known as shown in the documents cited in the international search report. It cannot hence be considered to be an important chemical structural element. Consequently, these groups of inventions are not considered to be so linked as to form a single general inventive concept.

Therefore, this application does not comply with the requirement of unity of invention.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	12, 18-20, 26, 27, 32	YES
	Claims	1-11, 13-17, 21-25	NO
Inventive step (IS)	Claims	12, 18, 26	YES
	Claims	1-11, 13-17, 19-25, 27, 32	NO
Industrial applicability (IA)	Claims	1-27, 32	YES
	Claims		NO

2. Citations and explanations

Document 1: EP 133244 A2 (E.I. Du Pont de Nemours and Company), 20 February 1985

Document 2: EP 362578 A1 (E.I. Du Pont de Nemours and Company), 11 April 1990

Document 3: Biochemical Pharmacology, (1990), Vol. 40, No. 4, pages 709 to 714

Document 4: WO 02/36568 A1 (Astrazeneca AB), 10 May 2002

Document 5: Periodicum Biologorum, (2001), Vol. 103, No. 4, pages 321 to 325

Document 6: Polish Journal of Pharmacology and Pharmacy, (1986), Vol. 38, No. 1, pages 115 to 124

Document 7: Bioorganic & Medicinal Chemistry, (2001), Vol. 9, No. 12, pages 3273 to 3286

Document 8: J. Med. Chem., (1998), Vol. 41, No. 12, pages 2029 to 2039

Document 9: US 5780634 A (The Green Cross Corporation), 14 July 1998

Document 10: WO 00/31037 A1 (Smithkline Beecham S.P.A.), 2 June 2000

Document 11: WO 02/44165 A1 (Glaxosmithkline SPA), 6 June 2002

Document 12: WO 02/38547 A1 (Glaxosmithkline SPA), 16 May 2002

Document 13: WO 97/19927 A1 (Smithkline Beecham S.P.A.), 5

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June 1997

Document 14: WO 97/19926 A1 (Smithkline Beecham S.P.A.), 5

June 1997

Document 15: WO 95/32948 A1 (Smithkline Beecham S.P.A.), 7

December 1995

Document 16: EP 755685 A1 (Meiji Seika Kaisha Ltd.) 29

January 1997

Document 17: WO 01/32170 A1 (Swope, David, M.), 10 May

2001

Document 18: J. Biol. Chem., (1999), Vol. 274, No. 26,

pages 18438 to 18445

Claims 1 to 8, 22 and 24

The invention set forth in claims 1 to 8, 22 and 24 lacks novelty and does not involve an inventive step in the light of documents 1 to 6 and 10 to 15 cited in the international search report.

Documents 1 to 3 set forth antitumor agents having as active ingredients the compounds set forth in one of claims 1 to 8 of this application, documents 4 to 6 set forth analgesics and/or antiinflammatory agents having as active ingredients the compounds set forth in one of claims 1 to 8 of this application, and documents 10 to 15 set forth agents for the treatment of disorders such as inflammation and allergies, hypertension, Huntington's disease, Alzheimer's disease, and Parkinson's disease, and having as active ingredients the compounds set forth in one of claims 1, 2, 4 and 8 of this international application. In addition, the description of this application indicates that the "phosphodiesterase 10A inhibitor" of this application is used as an agent for the treatment and/or prevention of disorders such as tumors, pain, inflammation, allergies, hypertension, Huntington's disease and Alzheimer's disease, and Parkinson's disease, therefore there is no difference between the invention set

forth in claims 1 to 8, 22 and 24 of this application and the inventions set forth in documents 1 to 6 and 10 to 15.

In addition, in the medical field it is common practice to modify compounds having pharmacological action as necessary, therefore it would be easy for a person skilled in the art to conceive of converting the substituted groups in the compounds described in documents 1 to 6 or 10 to 15 as necessary, and verifying their pharmacological action.

Claims 9 to 11 and 13 to 15

The invention set forth in claims 9 to 11 and 13 to 15 lacks novelty and does not involve an inventive step in the light of documents 4 to 11 cited in the international search report.

Documents 4 to 11 set forth the compounds described in either claims 9 to 11 or 13 to 15 of this application.

In addition, in the medical field it is common practice to modify compounds having pharmacological action as necessary, therefore it would be easy for a person skilled in the art to conceive of converting the substituted groups in the compounds described in documents 4 to 6 or 10 to 15 as necessary, and verifying their pharmacological action.

Claim 12

The invention set forth in claim 12 is novel and involves an inventive step in relation to the documents cited in the international search report.

Documents 1 to 18 do not disclose the compound described in claim 9 of this application, which is piperazine-1-yl having an unsubstituted alaryl or R3A substituted at the fourth position in the general formula (IA), and it would not be easy for a person skilled in the art to conceive of said compound in the light of documents

1 to 18.

Claims 16, 17, 21, 23 and 25

The invention set forth in claims 16, 17, 21, 23 and 25 lacks novelty and does not involve an inventive step in the light of documents 4 to 6 cited in the international search report.

Documents 4 to 6 set forth analgesics and/or antiinflammatory agents having as active ingredients the compounds set forth in one of claims 9, 13 and 14 of this application.

Moreover, the invention set forth in claims 16, 17, 21, 23 and 25 does not involve an inventive step in the light of documents 1 to 6 cited in the international search report.

In the medical field it is common practice to modify compounds having pharmacological action as necessary, therefore it would be easy for a person skilled in the art to conceive of converting the substituted groups in the compounds described in documents 1 to 6 as necessary, and verifying their pharmacological action.

Claims 18 and 26

The invention set forth in claims 18 and 26 lacks novelty and does not involve an inventive step in the light of the documents cited in the international search report.

Documents 1 to 18 do not indicate that the compounds set forth in one of claims 9 to 15 are effective in the treatment and/or prevention of dyskinesia, and it would not be easy for a person skilled in the art to conceive of said feature in the light of documents 1 to 18.

Claims 19 and 27

The invention set forth in claims 19 and 27 is not

disclosed in any of the documents cited in the international search report, and is novel, but does not involve an inventive step in the light of documents 1 to 3 cited in the international search report.

Documents 1 to 3 set forth antitumor agents containing as active ingredients compounds which have a similar structure to the compounds set forth in claims 9 to 15. In the medical field it is common practice to modify compounds having pharmacological action as necessary, therefore it would be easy for a person skilled in the art to conceive of converting the substituted groups in the compounds described in documents 1 to 3 as necessary, and verifying their pharmacological action.

Claims 20 and 32

The invention set forth in claims 20 and 32 is not disclosed in any of the documents cited in the international search report, and is novel, but does not involve an inventive step in the light of documents 16 to 18 cited in the international search report.

Documents 16 and 17 indicate that compounds having a phosphodiesterase inhibiting function are effective in the treatment of dyskinesia, and document 16 indicates that it is conceivable that dyskinesia symptoms may be brought about by a reduction of the cAMP amount within brain cells, therefore by inhibiting phosphodiesterase, which is an enzyme which hydrolyzes cAMP, the cAMP concentration within the brain is increased. Document 18 sets forth phosphodiesterase 10A as one phosphodiesterase which hydrolyzes cAMP, therefore it would be easy for a person skilled in the art to conceive of applying a compound having a phosphodiesterase 10A inhibiting effect to the treatment and/or prevention of dyskinesia.

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VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
US 2003/0018047 A1	23 January 2003 (23.01.2003)	03 May 2002 (03.05.2002)	20 April 2001 (20.04.2001)

[EX]

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)